NEUROENDOCRINOLOGY

New regulator of leptin signalling

Hdac5 (which encodes histone deacetylase 5) is expressed in specific hypothalamic neurons that are activated by leptin. Using a combination of mouse and *in vitro* experiments, investigators have shown that HDAC5 regulates the post-translational modification of signal transducer and activator of transcription 3 (STAT3), a known target of leptin signalling.

In mice fed a high-fat diet (HFD) the team found that hypothalamic expression of *Hdac5* was decreased and, in leptin-deficient obese mice, reintroduction of leptin normalized *Hdac5* expression. Moreover, *Hdac5* expression was not increased when the mice were fed a fat-free diet after a period of fasting, which indicates

that both leptin and dietary lipids can regulate the gene's expression. *Hdac5* knock-out mice also had greater weight gain in response to an HFD than wild-type mice, which resulted from hyperphagia.

As leptin activates *Pomc*-expressing neurons in the hypothalamus, the researchers also looked at transcriptional changes in these cells. In *Hdac5* knock-out mice, the leptin target gene *Stat3* was downregulated. When HDAC5 levels were reduced, STAT3 acetylation was increased, which led to changes in subcellular localization of the transcription factor and diminished *Pomc* expression. Importantly, HDAC5 was found to physically interact with STAT3 using co-immunoprecipitation assays.

These results indicate that HDAC5 is a key component of the leptin signalling pathway.

Finally, the investigators found that overexpression of *Hdac5* in the hypothalamus improved leptin sensitivity in HFD-fed mice, and reduced obesity and fat mass in diet-induced obese mice. Taken together, these findings highlight a mechanism of HDAC5-mediated STAT3 modification, which could be used therapeutically to 'fine-tune' leptin signalling in metabolic disorders and obesity.

Tim Geach

ORIGINAL ARTICLE Kabra, D. G. *et al.*

Hypothalamic leptin action is mediated by histone deacetylase 5. *Nat. Commun.* **7**, 10782 (2016)